37 PRELIMINARY STUDIES ON THE IN VIVO DESENSITIZATION OF CENTRAL NICOTINIC RECEPTORS BY (-)-NICOTINE.

Heidi F. Villanueva, John A. Rosecrans and Shawali Arezo
Department of Pharmacology and Toxicology, Va. Commonwealth Univ.-Medical College of Va., MCV Box 613, Richmond, VA 23298-0613, USA

Evidence for desensitization of the nicotinic receptor via nicotine has been suggested from two recent studies in this laboratory. The first study utilized a standard two-lever operant drug discrimination procedure. Rats were trained to discriminate 0.4 mg/kg (-)-nicotine from saline on a VI-15 second schedule of food reinforcement. When nicotine administration was preceded by an additional 0.4 mg/kg dose of nicotine, responding on the drug-appropriate lever was decreased in a sub-population of rats. The peak effect of the desensitization varied for individual rats and ranged from 15 minutes to 3 hours.

The second study examined the ability of (-)-nicotine to protect cholinergic receptors from an acetylcholinergic neurotoxin, AF64A (Ethylcholine aziridinium ion). The basic hypothesis is that nicotine might spare cholinergic receptors from AF64A via a desensitization of these neurons presynaptically. Rats were trained to perform a short-term memory task in an eight arm radial maze. Following training, rats were implanted with 14 day Alzet osmotic mini pumps containing (-)-nicotine (1.5 mg/day) or saline. Seven days after pump implantation, rats were injected intraventricularly (ivt) with 6 ng AF64A or with distilled water. All animals were tested for short-term memory deficits seven days after ivt injections. Animals receiving distilled water displayed no memory deficits, while those receiving AF64A following pre-treatment with saline displayed significant deficits. Animals infused with nicotine prior to receiving AF64A showed moderate memory deficits, suggesting that nicotine may have partially desensitized acetylcholinergic receptors, thus preserving some short-term memory ability. Further studies in this laboratory will attempt to determine the possible mechanisms of desensitization of nicotinic receptors by nicotine.